REMARKS

Status of the Claims

Claims 1-2, 6-8, 16-30, and 37-39 are pending. Claims 1, 2, 6, and 37-39 are amended. Claims 7 and 8 are withdrawn. Claims 31-33 are canceled herein without prejudice or disclaimer. Support for the amended claims can be found throughout the specification and in the claims as originally filed.[1]

Title

The USPTO objects to the application's title. As per the USPTO's suggestion, Applicants have amended the title to recite "cardiomyocytes" rather than "terminal differentiated cells." Accordingly, the objection has been overcome.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4, 6, 16-33, and 37-39 stand rejected under 35 U.S.C. § 112, 1st paragraph, because the specification, while being enabling for a method of proliferating cardiomyocytes *in vitro* and *in vivo* comprising introducing nucleotide sequences coding for a nuclear localization signal, D-type cyclin gene (D1, D2, or D3) and a cyclin dependent kinase gene (CDK4 or CDK6) directly into the cardiomyocytes using an adenoviral expression vector, allegedly does not reasonably provide enablement for a method of proliferating cardiomyocytes using any vector for introducing the recited nucleotide sequences.[2]

Applicants respectfully traverse.

A. The claims do not encompass the embodiments suggested by the USPTO.

The USPTO contends that the claims encompass any vectors including "bacterial shuttle vectors having no eukaryotic promoters" and that "the claimed cyclin and CDK genes and the nuclear localization signal are not operably linked to any eukaryotic promoter."[3]

As amended, the claims are directed to methods of proliferating cardiomyocytes comprising introducing various nucleic acids directly into cardiomyocytes using a viral vector and expressing

[1] *See, e.g.*, Specification, ¶¶ [050] and [077].

[2] *See* Office Action, page 3.

[3] *See id.* at page 4.

these nucleic acids in the cardiomyocytes.[4] As such, one of skill in the art would understand that the claims do not encompass the potentially inoperative embodiments suggested by the USPTO (e.g., bacterial shuttle vectors having no eukaryotic promoters). Indeed, constructs that do not result in expression are outside the claims. Accordingly, this aspect of the enablement rejection should be withdrawn.

B. The USPTO fails to establish a *prima facie* enablement rejection.

In its previous response, Applicants argued that the USPTO failed to establish a *prima facie* enablement rejection.[5] In particular, the USPTO did not provide any evidence to support its rejection. Applicants also pointed out that the evidence of record including the Declaration of Dr. Koshimizu under 37 C.F.R. § 1.132, demonstrated that viral vectors were well known and used in the art, at the time of filing, for successfully delivery of genes into cardiomyocytes.

The USPTO now cites Gojo et al.—a post-filing date reference—to support its rejection. Among other things, the USPTO contends that this reference teaches that all retroviruses are unable to infect non-dividing cells.[6]

Applicants respectfully submit that Gojo et al. does not support the USPTO's rejection. Rather, this article supports Applicants' position that viral vectors were well known and useful in delivering genes to cells such as cardiomyocytes. Indeed, Gojo et al. states:

- "Advances in techniques have resulted in practical applications for gene therapy…"[7]
- "…viruses can be powerful vehicles to introduce therapeutic genes into human cells."[8]
- "Viral vectors are more efficient [than non-viral methods]"[9]
- "Lentiviruses … infect quiescent non-dividing cells."[10]

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[4] As demonstrated in the exemplified embodiments, one of skill in the art would understand that at least two viral vectors may be used to co-transfect the genes of interest into the cardiomyocytes. *See, e.g.*, Specification, Examples 1 and 5.

[5] *See* Applicants' response, filed June 9, 2009 ("Applicants' response"), pages 6-7.

[6] *See* Office Action, page 4.

[7] Gojo et al., abstract.

[8] *Id.* at page 297.

[9] *Id.* at page 298.

- "Lentiviral or certain other retroviral vectors offer potential for treatment of a wide variety of diseases, including … cardiovascular diseases. Potential target cells include … cardiomyocytes."[11]

Accordingly, Applicants maintain that the USPTO fails to establish a *prima facie* case of non-enablement.

C. The full scope of the claimed invention is enabled

In its previous response, Applicants explained that the evidence of record including Dr. Koshimizu's Declaration and previously issued U.S. patents demonstrate that the use of viral vectors are enabled.[12]

1. Dr. Koshimizu's declaration provides evidence of using retroviral vectors.

The USPTO contends that (i) the claims encompass a bacterial shuttle vector having no eukaryotic expression elements and none of the references cited by Dr. Koshimizu teach such constructs; and (ii) the only cited art relevant to retroviral gene transfer fails to exemplify using a retrovirus and is directed to non-dividing cells.[13]

First, as discussed above, the claims have been amended to recite that the nucleic acids are introduced and expressed in the cardiomyocytes. As such, one of skill in the art would understand that the claims do not encompass the potentially inoperative embodiments suggested by the USPTO (e.g., bacterial shuttle vectors having no eukaryotic promoters).

Second, at least two references cited by Dr. Koshimizu specifically teach the use of retroviral vectors in non-dividing cells. Indeed, Sakoda et al. teaches "the efficient transduction of non-dividing cells, including post mitotic beating rat cardiac myocytes and well differentiated rat L6 myofibers" using the retrovirus *Lentivirus* as a vector.[14] Moreover, Mochizuki et al. teaches successful transduction of rat cardiac myocytes using an HIV-1 retroviral vector system and concludes that this vector system is "efficient, robust, and safe."[15]

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[10] *Id.*

[11] *Id.*

[12] *See* Applicants' response, pages 7-8.

[13] *See* Office Action, page 4.

[14] *See* Declaration of Dr. Koshimizu, ¶ 24.

[15] *See id.* at ¶ 25.

2. The issued patents provide evidence of the state of the art.

The USPTO asserts that the identification of issued patents is not persuasive because each patent application is examined on its on merits.

Applicants appreciate the USPTO's comment, but again point out that the cited patents are evidence of at least the state of the art—a *Wands* factor.[16] Indeed, these patents demonstrate that the use of vectors (including non-adenoviral vectors) in cardiovascular-related methods were well known at the time of filing the instant application.

In view of the foregoing, Applicants submit that the full scope of the claimed invention is enabled. Accordingly, Applicants respectfully request withdrawal of this rejection.

D. Claims 6 and 39 are allowable.

Claims 6 and 39 are directed to the methods of claims 2 and 1, respectively, where the recited genes are transferred into cardiomyocytes via an adenovirus vector. The USPTO indicates that such methods are enabled.[17] As such, Applicants again respectfully request an indication that at least claims 6 and 39 are allowable.[18]

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[16] *See* Applicants' response, page 8 ("…the cited patents are evidence of at least the state of the art—a *Wands* factor.")

[17] *See* Office Action, pages 3-4.

[18] *See* Applicants' response, page 9 ("Applicants respectfully request an indication that at least claims 6 and 39 are allowable.").

CONCLUSION

It is believed that these amendments and remarks should place this application in condition for allowance. A notice to that effect is respectfully solicited. If the Examiner has any questions relating to this response or the application in general he is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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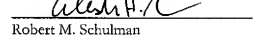
By: 

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